required under this section to be reported, including raw data and any correspondence relating to the adverse drug experiences, and the records required to be maintained under paragraph (c)(4) of this section.

(2) Manufacturers and packers may retain the records required in paragraph (f)(1) of this section as part of its complaint files maintained under § 211.198 of this chapter.

(3) Manufacturers, packers, and distributors shall permit any authorized FDA employee, at all reasonable times, to have access to and copy and verify the records established and maintained under this section.

(g) *Disclaimer.* A report or information submitted by a manufacturer, packer, or distributor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer, packer, or distributor, or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. The manufacturer, packer, or distributor need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.

[51 FR 24479, July 3, 1986, as amended at 52 FR 37936, Oct. 13, 1987; 55 FR 11578, Mar. 29, 1990; 57 FR 17980, Apr. 28, 1992; 62 FR 34167, June 25, 1997; 62 FR 52249, Oct. 7, 1997; 67 FR 9585, Mar. 4, 2002]

## Subpart E—Requirements for Specific New Drugs or Devices

### § 310.500 Digoxin products for oral use; conditions for marketing.

(a) Studies have shown evidence of clinically significant differences in bioavailability in different batches of certain marketed digoxin products for oral use from single manufacturers as well as in batches of these products produced by different manufacturers. These differences were observed despite the fact that the products met compendial specifications. Other studies have shown that there is a sufficient correlation between bioavailability in vivo and the dissolution rate of digoxin tablets in vitro to make the dissolution test an important addition to the compendial standards. Because of the potential for serious risk to cardiac patients using digoxin products which may vary in bioavailability, the Commissioner of Food and Drugs has determined that immediate action must be taken to assure the uniformity of all digoxin products for oral use. The Commissioner is of the opinion that digoxin products for oral use are new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which approved new drug applications are required. The Commissioner has determined that, because of questions raised regarding the bioavailability of digoxin products for oral use, there is sufficient evidence to invoke the authority under section 505(j) of the act to fully investigate this question and to facilitate a determination of whether there is a ground for withdrawal of approval of the drug product under section 505(e) of the act. Marketing of these products may be continued only under the following conditions:

(1) Digoxin products for oral use, other than tablets: Any person marketing digoxin products for oral use, other than tablets, shall submit to the Food and Drug Administration on or before February 21, 1974, an abbreviated new drug application for these products. Any such drug product then on the market which is not the subject of an application submitted for the drug product shall be subject to regulatory procedures under section 505 of the act. In addition to the information specified in § 314.50 of this chapter, the application shall contain:

(i) A full list of the articles used as components of the digoxin product, specifications for components, detailed identification and analytical procedures used to assure that the components meet established specifications of identity, strength, quality, and purity and a complete description of the manufacturing process.

(ii) The source of the digoxin used in the formulation including the name and address of the supplier.

(iii) A statement that stability studies will be conducted to establish a suitable expiration date for the digoxin

product in the form in which it is distributed.

(iv) A statement that the product label will contain a suitable expiration date. In the absence of any stability test data, this expiration date shall be no longer than one year after the batch is manufactured. If the expiration date is greater than one year, supporting stability data shall be included in the application.

(v) Labeling that is in compliance with all requirements of the act and regulations promulgated thereunder, the pertinent parts of which are as indicated in paragraph (e) of this section.

(vi) A statement that the applicant will initiate recall of all stocks of the drug product outstanding when so requested by the Food and Drug Administration.

(vii) A statement that the applicant intends to conduct in vivo bioavailability tests and that the applicant, under the records and reports provisions of section 505(k) of the act, will:

(*a*) Within 30 days after the submission of the application, submit to the Food and Drug Administration the protocol which the applicant proposes to follow in conducting these in vivo bioavailability tests. The protocol shall contain all of the essential elements set forth in paragraph (d) of this section. The tests shall not be initiated prior to receiving notification from the Food and Drug Administration that the bioavailability protocol has been reviewed and either approved or its deficiencies delineated.

(*b*) Within 180 days after receiving notification from the Food and Drug Administration that the bioavailability protocol has been reviewed, submit to the Food and Drug Administration the results of the in vivo bioavailability tests.

(2) Digoxin tablets: Any person marketing digoxin tablets, in addition to complying with all of the requirements of paragraph (a)(1) of this section, shall include in their abbreviated new drug application:

(i) A statement that the applicant will establish procedures to test each lot of digoxin tablets prior to releasing the batch for distribution to assure that the batch meets all of The United States Pharmacopeia (USP XVIII) requirements for digoxin tablets including, but not limited to, potency, content uniformity, and dissolution and either (*a*) that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or (*b*) that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

(ii) A statement that finished product specifications shall be established to include provisions to assure that the range of average one-hour dissolution values among batches of digoxin tablets does not exceed 20 percent.

(3) Before releasing for distribution any batch of digoxin tablets manufactured after January 22, 1974, the manufacturer shall:

(i) Test a sample of the batch to assure that the batch meets all of the requirements of The United States Pharmacopeia (USP XVIII) including but not limited to, potency, content uniformity, and dissolution and either (*a*) that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or (*b*) that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

(ii) Submit a sample of the batch to the Food and Drug Administration according to the procedures set forth in paragraph (g) of this section. Results of tests conducted on the batch by or for the manufacturer and the batch production record shall accompany the sample.

(iii) Withhold the batch from distribution until he is notified by the Food and Drug Administration that the sample was tested and found to meet all of the requirements in The United States Pharmacopeia (USP XVIII) for potency, content uniformity, and dissolution and either (*a*) that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or (*b*) that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

(iv) Submit a sample of each batch of digoxin tablets as provided for in paragraph (a)(3)(ii) of this section until he

is notified by the Food and Drug Administration that he is released from the certification program. This notification will be made on the basis of sample test results, inspectional findings regarding compliance with current good manufacturing practice, and compliance with all other requirements of this section and any other directives issued by the Food and Drug Administration as a condition for release from the certification program.

(4) Any manufacturer who has distributed any batch of digoxin tablets which does not meet the compendial requirement for dissolution, when tested by the method in The United States Pharmacopeia (USP XVIII), shall initiate recall of the subject batch when so requested by the Food and Drug Administration.

(b) Failure of an applicant to submit the protocol and/or the results of the in vivo bioavailability tests showing adequate evidence of the product's bioavailability within the times specified in paragraph (a)(1)(vii) of this section and/or to comply with all of the certification requirements of paragraph (a)(3) of this section shall be justification for withdrawal of approval of the application under section 505(e) of the act.

(c) Any product reformulation or change in manufacturing process will require the submission of a supplement to the approved abbreviated new drug application containing adequate data to demonstrate the bioavailability of the reformulated product. Food and Drug Administration approval of the supplement is required before the reformulated product is marketed. The Food and Drug Administration recommends that, where digoxin tablets are reformulated, manufacturers reformulate their product to achieve dissolution of 70 to 90 percent at one hour when tested by all three methods (i.e., the USP method, and the ''paddle-water'' and ''paddle-acid'' methods) described in paragraph (h) of this section.

(d) The protocol for the in vivo bioavailability tests required in paragraphs (a) and (c) of this section shall employ a three-way crossover design using the digoxin test product; a reference digoxin tablet supplied, on request, by the Food and Drug Administration; and bulk digoxin USP in an oral solution. Appropriate venous blood and urinary samples are to be collected and analyzed. The method shall be capable of detecting the difference between the reference tablet and the reference oral solution. Bioavailability of the test product shall be demonstrated if a mean absorption of at least 75 percent of the combined mean of the two reference standards is observed. Assistance in developing a protocol for a particular dosage formulation may be obtained by contacting the Food and Drug Administration, Center for Drug Evaluation and Research (HFD–420), 5600 Fishers Lane, Rockville, MD 20857.

(e) Parts of the digoxin product labeling indicated below shall be as follows:

DIGOXIN LABELING GUIDANCE

(ADULT AND PEDIATRIC)

DESCRIPTION

Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific and powerful effects on the myocardium. These drugs are found in a number of plants. The term ''digitalis'' is used to designate the whole group. Typically, the glycosides are composed of three portions: a steroid nucleus, a lactone ring, and a sugar (hence ''glycosides'').

(This section should include a chemical and physical description of digoxin and the same quantitative ingredient information as that required on the label.)

ACTION

The digitalis glycosides have qualitatively the same therapeutic effects on the heart. They (1) increase the force of myocardial contraction, (2) increase the refractory period of the atrioventricular (A–V) node, and (3) to a lesser degree, affect the sinoatrial (S–A) node and conduction system via the parasympathetic and sympathetic nervous systems.

Gastrointestinal absorption of digoxin is a passive process. About 50–75 percent of digoxin in tablet form is absorbed. Digoxin is only 20–25 percent bound to plasma proteins and is predominantly excreted by the kidneys unmetabolized unless there is significant renal failure. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass, presumably because of tissue binding. In subjects with normal renal function, digoxin is excreted exponentially with an average half-life of 36

hours, resulting in the loss of 35–40 percent of the body stores daily.

Serum levels and pharmacokinetics are essentially unchanged by massive weight loss, suggesting that lean body mass should be used in dosage calculations. The peak blood level from oral dosing with tablets occurs 1–3 hours after administration. The onset of therapeutic action of digoxin after oral tablets is 1–2 hours, with the peak therapeutic effect occurring 6–8 hours after dosing.

INDICATIONS

1. Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in ''low output'' failure and less effective in ''high output'' (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated.

Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter. Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia. Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock. The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram negative bacteria.

CONTRAINDICATIONS

The presence of toxic effects (See ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the gylcosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS

Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications on digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. See ACTION section for mechanism.

PRECAUTIONS

Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin, and toxicity may develop even with the usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteriod therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as

described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A–V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constructive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin, and dosage must be adjusted accordingly in patients with renal disease. NOTE: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

ADVERSE REACTIONS

Gynecomastia, uncommon.

Overdosage or toxic effects.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage. Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES

Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4–6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40–100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

CAUTION: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

DOSAGE AND ADMINISTRATION

Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0–1.5 milligrams. Digitalization may be accomplished by any

of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5–0.75 milligram orally usually produces a detectable effect in 1–2 hours that becomes maximal in 6–8 hours. Additional doses of 0.25–0.5 milligram may be given cautiously at 6–8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125–0.5 milligram, see next paragraph) without a loading dose results in development of a steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125–0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125–0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged (see ACTION section). Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

(If pediatric dosage is available, the labeling sections above should be expanded to include the following information.)

PEDIATRIC INFORMATION

WARNINGS

Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

NOTE: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS

Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A–V block particularly are more common manifestations of toxicity in children. Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES

(See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1–1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less per 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION

Digitalization must be individualized. Generally, premature and immature infants are

particularly sensitive, requiring reduced dosage that must be determined by careful titration.

*Oral Dosage*. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40–60 micrograms/kilogram.

Infants, 1 month to 2 years, require approximately 60–80 micrograms/kilogram.

Children 2 years to 10 years, require 40–60 micrograms/kilogram.

Children, over 10 years of age, require adult dosages in proportion to their body weight.

Maintenance therapy is 20–30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

(f) Abbreviated new drug applications shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, 5600 Fishers Lane, Rockville, MD 20857.

(g) All samples of digoxin tablets required by paragraph (a)(3) of this section to be submitted to the Food and Drug Administration shall be handled as follows:

(1) The sample shall consist of 6 subsamples of 1000 tablets each collected at random from throughout the manufacturing run. Each of the 6 subsamples shall be identified with the name of the product, the labeled potency, the date of manufacture, the batch number, and the name and address of the manufacturer.

(2) The sample together with the batch production record and results of all tests conducted by or for the manufacturer to determine the product's identity, strength, quality, and purity, content uniformity and dissolution shall be submitted to the Department of Health and Human Services, Public Health Service, FDA National Center for Drug Analysis, 1114 Market St., St. Louis, MO 63101. The outer wrapper shall be identified ''SAMPLE—DIGOXIN CERTIFICATION.''

(h) The Food and Drug Administration is aware of data with two in vitro methods, in addition to that described in The United States Pharmacopeia (USP XVIII), developed to measure digoxin tablets dissolution. These two methods, the so-called ''paddle-water'' and ''paddle-acid'' methods, are described below and are identical with the exception of the nature of the dissolution medium used in the procedures (i.e., distilled or deionized water vs. dilute hydrochloric acid (0.6 percent volume/volume)). The dissolution apparatus used in these two methods differs significantly from the apparatus described in the method in the compendium. The Food and Drug Administration is aware that the three methods (i.e., USP, ''paddle-water,'' and ''paddle-acid'') show significant differences in dissolution in comparative tests on some formulations. Definitive bioavailability data to compare the relative value of each of these methods to predict bioavailability of the few formulations where the methods show significant differences in dissolution rate are not now available. Manufacturers who conduct research utilizing the ''paddle-water'' and ''paddle-acid'' methods, particularly in comparison with the method in The United States Pharmacopeia, shall submit any data obtained using these methods to the Food and Drug Administration pursuant to section 505(k) of the act.

(1) *Dissolution apparatus.*

(NOTE: Throughout this procedure use scrupulously clean glassware, which previously has been rinsed with dilute hydrochloric acid, distilled or deionized water, then with alcohol, and carefully dried. Take precautions to prevent contamination from airborne, fluorescent particles and from metal and rubber surfaces.) The apparatus consists of a suitable water bath, a 1000 milliliter glass vessel (Kimble Glass No. 26220 or equivalent), a motor, and a polytetrafluoroethylene stirring blade (Sargent S–76637, Size B, 3 inch length; or equivalent) on a glass stirring shaft (Sargent 5–76636, 14.5 inch length; or equivalent). The water bath may be of any convenient size that permits keeping the water temperature uniformly at 37° C. ±0.5° C. throughout the test. The vessel is spherical, and is provided with three ports at the top, one of which is centered. The lower half of the vessel is 65 millimeters in inside

radius and the vessel's nominal capacity is 1000 milliliters. The glass stirring shaft from the motor is placed in the center port, and one of the outer ports may be used for insertion of a thermometer. Samples may be removed for analysis through the other port. The motor is fitted with a speed-regulating device that allows the motor speed to be held at 50 rpm ±2 rpm. The motor is suspended above the vessel in such a way that it may be raised or lowered to position the stirring blade. The glass stirring shaft is 10 millimeters in diameter and about 37 centimeters in length. It must run true on the motor axis without perceptible wobble. The polytetrafluoroethylene stirring blade is 4 millimeters thick and forms a section of a circle, whose diameter is 83 millimeters and which is subtended by parallel chords of 42 and 77 millimeters. The blade is positioned horizontally, with the 42-millimeter edge down, 2.5 centimeters ±0.2 centimeter above the lowest inner surface of the vessel.

(2) *Reagents*—(i) *Dissolution medium.* For ''paddle-water,'' use distilled or deionized water. For ''paddle-acid,'' use dilute hydrochloric acid (0.6 percent volume/volume). Use the same batch of dissolution medium throughout the test.

(ii) *Standard solutions.* Accurately weigh approximately 25 milligrams of The United States Pharmacopeia Digoxin Reference Standard, dissolve in a minimum amount of 95 percent ethanol in a 500 milliliter volumetric flask and add 95 percent ethanol to volume and mix. Dilute 10.0 milliliters of this first solution to 100.0 milliliters with 95 percent ethanol and mix for the second solution. Just prior to use, individually dilute 1.0, 2.0, 3.0, 4.0, and 5.0 milliliter aliquots of the second solution with dissolution medium to 50.0 milliliters. These solutions are equivalent to 20, 40, 60, 80, and 100 percent of dissolution, respectively, for a 0.25 milligram digoxin tablet.

(iii) *Extraction solvent.* Prepare a solvent containing 6 volumes of chloroform, analytical reagent grade, with 1 volume of n-propyl alcohol, analytical reagent grade.

(iv) *Ascorbic acid-methanol solution.* Prepare a solution containing 2 milligrams of ascorbic acid, analytical reagent grade, per 1 milliliter of methanol, absolute, analytical reagent grade.

(v) *Hydrochloric acid, concentrated reagent grade.*

(vi) *Hydrogen peroxide-methanol solution.* On the day of use, dilute 2.0 milliliters of recently assayed 30 percent hydrogen peroxide, reagent grade, with methanol, absolute, analytical reagent grade to 100.0 milliliters. Store in a refrigerator. Just prior to use, dilute 2.0 milliliters of this solution with methanol to 100.0 milliliters.

(3) *Procedure*—(i) *Dissolution.* Place 500 milliliters of dissolution medium in the vessel, immerse it in the constant-temperature bath set at 37°C.±0.5°C., and allow the dissolution medium to assume the temperature of the bath. Position the shaft so that there is a distance of 2.5 centimeters ±0.2 centimeter between the midpoint of the bottom of the blade and the bottom of the vessel. With the stirrer operating at a speed of 50 rpm±2 rpm, place 1 tablet into the flask. After 60 minutes, accurately timed, withdraw 25 milliliters, using a glass syringe connected to a glass sampling tube, of solution from a point midway between the stirring shaft and the wall of the vessel, and approximately midway in depth. Filter the solution promptly after withdrawal, using a suitable membrane filter of not greater than 0.8 micron porosity (Millipore AAWP 025 00, or equivalent), mounted in a suitable holder (Millipore Swinnex SX00 025 00, or equivalent), discarding the first 100 milliliters of filtrate. This is the test solution. Repeat the dissolution procedure on 5 additional tablets.

(ii) *Extraction.* Transfer 10.0 milliliters of each of the six filtrates, 10.0 milliliters of each of the five standard solutions, and 10.0 milliliters of dissolution medium, to provide a blank, in separate 60-milliliter separators. Extract each solution with two 10-milliliter portions of extraction solvent. Combine the extracts of each solution in separate, glass-stoppered, 50-milliliter conical flasks, and evaporate on a steam bath with the aid of a stream of nitrogen to dryness, rinsing the sides of the flasks with extraction solvent. Take care to ensure that all traces of solvent are removed, but avoid prolonged heating. For convenience the residues may be stored in a vacuum desiccator overnight.

(iii) *Measurement of fluorescence.* Begin with the standard solutions, and

keep all flasks in the same sequence throughout, so that the elapsed time from addition of reagents to reading of fluorescence is the same for each. Carry the test solutions, standard solutions, and the blank through the determination in one group. Add the following three reagents in as rapid a sequence as possible, swirling after each addition, treating 1 flask at a time, in the order named: 1.0 milliliter of ascorbic acid-methanol solution, 3.0 milliliters of concentrated hydrochloric acid, and 1.0 milliliter of hydrogen peroxide-methanol solution. Insert the stoppers in the flasks, and after 2 hours, measure the fluorescence at about 485 millimicrons, using excitation at about 372 millimicrons. In order to provide a check on the stability of the fluorometer, reread one or more standard solutions. Correct each reading for the blank and plot a standard curve of fluorescence versus precentage dissolution. Determine the percentage dissolution of digoxin in the test solutions by reading from the standard graph.

(iv) Digoxin tablets formulated so that the quantity of digoxin dissolved at one hour, when tested by the method in The United States Pharmacopeia (USP XVIII), is greater than 95 percent of the assayed amount of digoxin and so that the quantity of digoxin dissolved at 15 minutes is greater than 90 percent of the assayed amount of digoxin are new drugs which may be marketed only with an approved full new drug application as provided for in § 314.50 of this chapter. The application shall include, but not be limited to, clinical studies establishing significantly greater bioavailability than digoxin tablets meeting compendial requirements and dosage recommendations based on clinical studies establishing the safe and effective use of the bioavailable digoxin product. Marketing of these digoxin products will be allowed only under a proprietary or trade name, established name, and labeling which differs from that used for digoxin tablets that meet all of the requirements in The United States Pharmacopeia (USP XVIII) and that are formulated so that either (a) the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or (b) the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin. New drug applications for these digoxin products shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Drug Evaluation I (HFD–100), 5600 Fishers Lane, Rockville, MD 20857.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 43137, Sept. 30, 1976; 41 FR 49482, Nov. 3, 1976; 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990; 65 FR 56479, Sept. 19, 2000]

### § 310.501 Patient package inserts for oral contraceptives.

(a) *Requirement for a patient package insert.* The safe and effective use of oral contraceptive drug products requires that patients be fully informed of the benefits and the risks involved in their use. An oral contraceptive drug product that does not comply with the requirements of this section is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. Each dispenser of an oral contraceptive drug product shall provide a patient package insert to each patient (or to an agent of the patient) to whom the product is dispensed, except that the dispenser may provide the insert to the parent or legal guardian of a legally incompetent patient (or to the agent of either). The patient package insert is required to be placed in or accompany each package dispensed to the patient.

(b) *Distribution requirements.* (1) For oral contraceptive drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) Patient package inserts for oral contraceptives dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first oral contraceptive and every 30 days thereafter, as long as the therapy continues.

(c) *Contents of patient package insert.* A patient package insert for an oral contraceptive drug product is required to contain the following:

(1) The name of the drug.